Insulin Lispro: A Critical Evaluation
Insulin Lispro: A critical evaluation

Vijay Shukla, B. Pharm, Ph.D
Nicolaas Otten, Pharm. D.
CCOHTA

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REVIEWERS

This report was reviewed by:

Dr. David C.W. Lau (FRCPC)
Chief, Division of Endocrinology and Metabolism
University of Ottawa Hospital and The Ottawa Hospital
Ottawa, Ontario

Dr. Hugh D. Tildesley (FRCPC)
Internal Medicine and Endocrinology
Vancouver, British Columbia
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1. Introduction

Lispro is a synthetic insulin analog which incorporates a slight modification in its amino acid sequence. This change leads to a more rapid subcutaneous (s.c.) absorption of the drug, while maintaining its biological effects. Ten units each of lispro and regular human insulin (Humulin-R) were given by s.c. injection to healthy volunteers in a glucose clamp study. The pharmacodynamic characteristics of each preparation are presented in Table 1.

### Table 1. Pharmacodynamics of Lispro Compared with Human Insulin in Healthy Volunteers

<table>
<thead>
<tr>
<th>Insulin Type</th>
<th>Onset*</th>
<th>Peak Action</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lispro</td>
<td>30-45 min</td>
<td>0.75-2.5 hr</td>
<td>3.5-4.75 hr</td>
</tr>
<tr>
<td>Regular (Humulin-R)</td>
<td>30-60 min</td>
<td>0.75-4.5 hr</td>
<td>5.0-7.5 hr</td>
</tr>
</tbody>
</table>

* Onset is defined as the time taken for insulin activity to reach 10% of its peak.

The above characteristics of lispro are intended to mimic the pattern of endogenous insulin release in response to a meal, and to minimize overall fluctuations in blood glucose levels. According to a recent study in patients with insulin dependent diabetes mellitus (type I), the optimal time for bolus insulin injection was 20 min before meals for regular insulin and immediately before meals for lispro. Lispro shifts the time at which patients are at most risk of hypoglycemia (from 3-12 hours to 1-3 hours post-dose), but it does not eliminate the risk. There are no apparent differences in adverse effects, immunologic potential, or the signs and symptoms associated with hypoglycemia between treatment with lispro and regular insulin.

2. Approved Indications

Lispro is indicated for:

C the treatment of patients with diabetes mellitus who require insulin for the maintenance of normal glucose homeostasis; and

C the initial stabilization of diabetes mellitus. Lispro can be used in conjunction with longer-acting human insulin.
3. **Advantages of Lispro Over Regular Insulin**

The reported advantages of lispro are:

- It lessens the rise in serum glucose after meals.
- Hypoglycemic episodes occur less frequently.
- The overall glycemic control is improved in patients with type I diabetes who require insulin pumps.

4. **Assessing the Evidence**

**Quality and Quantity of Information Available**

Studies carried out to date have typically been unblinded, multicentre, randomized, parallel or crossover or sequential trials.\(^3\)\(^-\)\(^15\) Tables 2 and 3 summarize published and unpublished studies, respectively, comparing lispro and regular human insulin (see appendix). Most of the studies were carried out by or through a multinational study group headed by the pharmaceutical manufacturer. Blinding of treatments has been difficult given the different dosing times for lispro versus regular insulin. Crossover designs were used to allow patients to act as their own controls. Study duration ranged from 2 to 12 months. Outcome measurement may have been affected in some situations due to inter-country differences in dietary habits and treatment practices of diabetes.\(^16\)

**Glycemic Control**

The evidence is consistent in both type I and type II diabetes that lispro injection decreases significantly the postprandial rise in serum glucose, as well as postprandial glucose excursions (pretest glucose subtracted from 1 and 2 hour postprandial values), compared to regular insulin therapy.\(^3\)\(^-\)\(^8\),\(^10\)\(^-\)\(^14\) Lispro controlled the postprandial plasma glucose concentrations significantly better than regular insulin in patients with type I and type II diabetes in different studies. The clinical significance of this effect of lispro has not been demonstrated.

HbA1c is a useful surrogate marker for long-term glycemic control.\(^17\),\(^18\) The Diabetes Control and Complication Trial (DCCT) was the definitive study that demonstrated a correlation between glycemic control, as assessed by levels of HbA1c, and the development and progression of diabetic microvascular complications.\(^18\),\(^19\) Levels of HbA1c reduced from approximately 9.0% in the control group to approximately 7.0% in the intensively treated group. This reduction resulted in the following outcomes after an average follow-up of 6.5 years (relative risk reduction overall; absolute risk reduction primary prevention/secondary prevention): development of retinopathy...
(63%; 3.6%/4.1%), occurrence of microalbuminuria (39%; 1.2%/2.1%) and occurrence of clinical neuropathy (60%; 6.7%/9.1%). (Note: clinical neuropathy analysis was done after 5 years on therapy.)

Lispro has not shown a consistent impact on long-term glycemic control, as assessed by HbA1c levels, in comparative studies with regular insulin. Eight studies have been unable to demonstrate significant decreases in HbA1c levels or total insulin requirements when both lispro and basal insulin doses were manipulated.3-5,7,8,10,12,13 A recent meta-analysis of clinical trials compared lispro and regular human insulin in type I and type II diabetes patients. The results also showed no significant difference in the ability of these two preparations to lower HbA1c levels.20

However, a few studies have found that lispro significantly decreased HgA1c levels more than regular insulin. This change occurred simultaneously with either a change in dietary habits or an increase in total insulin daily dose. In a recent open label sequential (12 wk + 12 wk) trial, 141 patients with type I diabetes were asked to reduce their between meal snack intake when switching from conventional human insulin to lispro.9 Their reduction in snack intake was compensated by transferring at least 50% of their snack carbohydrate calories intake to the preceding main meal. On an intention-to-treat analysis, mean HbA1c was not significantly lower at the completion of the lispro treatment period compared with the human insulin period. In a subgroup analysis of the patients who were compliant with dietary changes, HbA1c levels decreased significantly (absolute reduction of 0.25%, p=0.014) at the end of treatment with lispro. However, less than half of the patients were fully compliant with the reduction of snacks in the study. Even if this decrease in HbA1c were true, more than 250 patients would need to start this regimen in order to avoid one case/year of worsening of retinopathy.18

In a 5-month open study, 66 patients with type I diabetes were switched over from regular human insulin to lispro as a pre-meal therapy.16 The mean HbA1c level decreased on average by 0.8% points during the 5-month study, and the value was significantly lower (p<0.001) than baseline after two months. However, this study was neither a crossover, parallel or sequential design. Furthermore, a significant increase in total insulin dosing may have caused the reduction in HgA1c rather than the switch to lispro. The total insulin dose increased by 7%.

Significant decreases in HbA1c levels with lispro treatment compared to regular human insulin were also observed in three unpublished open label studies in type I diabetes patients.11,14,15 Since these studies are published in abstract form only, it is not possible to estimate how much of the improvement in glycemic control and HbA1c is due to lispro, how much is due to associated changes in basal insulin, or how much due is due to the intensive attention the patients were given during the study.

Patients have not been followed in any studies for a sufficient period of time to measure improvements in outcomes related to micro vascular disease (i.e. retinopathy, nephropathy, neuropathy). This is to be expected, as HbA1c is a reflection of overall long-term glycemic control, which includes fasting and postprandial glucose excursion.17,18

Hypoglycemia
High incidences of hypoglycemia occur with intensive insulin treatment using regular human insulin. It is one of the main limiting factors for subjects and caregivers to achieve better glucose control. In the DCCT, long-term intensive insulin treatment (average follow-up of 6.5 years) significantly increased the frequency of severe hypoglycemia by three-fold. In this trial, severe hypoglycemia was defined as an event with symptoms consistent with hypoglycemia in which the patient required the assistance of another person, and which was associated with a blood glucose (B.G.) level <2.8 mmol/L or prompt recovery after oral carbohydrates, intravenous glucose or glucagon administration.

The incidence of non-severe and severe hypoglycemic episodes were recorded separately in most of the studies comparing lispro and regular human insulin. The definition of a hypoglycemic episode varies from study to study. In most of the studies the definition of a symptomatic severe hypoglycemic episode is similar to that in the DCCT trial. The biochemical definition of severe hypoglycemia i.e. B.G. <2.8 mmol/L, is not included in most of the studies.

**Hypoglycemia in Intensive Insulin Therapy**

Two 3-month studies compared the efficacy and safety of continuous s.c. infusion of lispro and regular insulin using an insulin pump. No significant difference in the frequency of hypoglycemia (B.G. <3 mol/L) per 30 days was observed. In one study there were no episodes of severe hypoglycemia as defined in DCCT trial. In another study, severe hypoglycemic episodes were reported three times in three patients with lispro and seven times in four patients with regular human insulin. In these episodes patients required external help to take sugar, but they never required glucagon or glucose injection. The rate of occurrences of very low blood glucose (<2 mmol/L) was significantly reduced with lispro (lispro, 0.05/month vs. regular human insulin, 0.47/month).

**Hypoglycemia in Regular Insulin Therapy**

Three studies compared regular insulin injection to lispro. Lispro significantly reduced hypoglycemic episodes in patients with type I diabetes. In these studies, a hypoglycemic episode was defined as a patient experiencing symptoms of hypoglycemia, if another person observed signs, or if B.G. level was below 3.5 mmol/L. In one of these studies, the value of B.G.<3.5 mmol/L for hypoglycemic event was used only for patients with newly diagnosed type I diabetes patients. A blood glucose level <2.0 mmol/L was considered as hypoglycemic in patients already using insulin. In a recent sequential study the number of hypoglycemic episodes (B.G. <2.5 mmol/L) was lower during treatment with lispro than with regular human insulin (lispro, 1.43/patient/10 week vs regular human insulin, 2.19/patient/10 week, p=0.004).
In these studies, episodes of symptomatic hypoglycemia were not differentiated from episodes of biochemical hypoglycemia i.e. B.G. levels less than set values. In patients with type II diabetes, no significant difference in the incidence of hypoglycemic episodes between lispro and regular human insulin was observed.\textsuperscript{5,6,8}

A meta-analysis of the clinical studies comparing lispro and regular human insulin did not show a significant difference in hypoglycemic rate/30 days between the two preparations in patients with type I or type II diabetes.\textsuperscript{20} In this meta-analysis, hypoglycemic episodes were defined as any time a patient: a) felt he or she was experiencing a sign or symptom of hypoglycemia; or b) had a blood glucose measurement $\leq 2$ mmol/L.

No significance difference was observed in the frequency of severe hypoglycemic episodes between lispro and regular human insulin, in any of the individual clinical trials with the exception of one.\textsuperscript{24} The lack of significant difference may be due to insufficient patient numbers and/or the length of follow-up in individual clinical trials. However in a recent meta-analysis, the incidences of severe hypoglycemic episodes were found to be significantly less in the lispro group compared to a regular human insulin group (3.1\% vs. 4.4\%, \textit{p}=0.024).\textsuperscript{25} This meta-analysis included three parallel and five crossover design multicentre clinical trials in patients with type I diabetes. Severe hypoglycemia was defined as a coma or requirement of glucagon or intravenous glucose. It should be noted that patients with a history of recurrent severe hypoglycemia were excluded from the trials included here. Therefore, the risks reported may under represent the general population of type I diabetic patients.

\textit{Insulin Pump Therapy}

Two short term studies (3 months) comparing the use of lispro and regular human insulin in insulin pump therapy are available. In both the studies lispro provided better glycemic control than regular insulin, without increasing the frequency of hypoglycemia. In a randomized, double blind crossover study, 30 patients with type I diabetes were treated with continuous infusion of either lispro or human regular insulin for three months.\textsuperscript{22} At the end of the three month period, HbA1c levels were significantly lower with lispro treatment (lispro, 7.66\% vs human insulin, 8.00\%, \textit{p}=0.0041). There was no significant difference between doses of lispro and regular human insulin. In another open label randomized, crossover multinational study, 39 patients with type I diabetes were treated for three months with continuous infusion of lispro. Lispro decreased HbA1c levels significantly more (-0.62\%) than the continuous infusion of regular human insulin (-0.09\%, \textit{p}=0.01).\textsuperscript{23}
5. Place in Therapy

It has been proposed that lispro would be of benefit to patients with unpredictable mealtimes to allow more schedule flexibility (convenience factor). More clinically-oriented applications may include use in patients with frequent episodes of postprandial hypoglycemia (to decrease their risk), patients with insulin resistance due to insulin antibodies (case reports only) and patients on continuous subcutaneous insulin infusion (CSII) therapy."
6. Economic Evaluation Studies

Quality of Life Evaluations

There is one published study conducted in four countries which evaluated the impact of lispro on quality of life (QOL), in both type I and type II diabetes patients. The authors appear to have created their own tool, and validation studies for the instrument have not been published. They concluded that lispro had a measurable impact on lifestyle benefits in type I diabetes patients, as reflected in improved treatment satisfaction and flexibility. These were the only two treatment differences detected in all domains evaluated in both type I and type II diabetes patients. The authors also reported variability in outcomes based on the patient’s country of origin, necessitating confirmation of the cross-cultural validity of this tool.

In another study, of the four primary domains of a quality of life questionnaire, significant improvement was observed for treatment satisfaction in patients treated with lispro compared with regular human insulin without any valid explanation. There were no differences between both treatments for the other three primary domains (energy/fatigue, health distress and treatment flexibility).

There are also three abstracts related to QOL issues which have been published to date. These studies concluded that patients perceived an improvement in their well-being and quality of life due to the freedom and flexibility of injections and improvement in hypoglycemic reactions. Patient convenience or preference has been cited as an advantage of lispro by many studies. However, measurement tools are either not elucidated in the reports, or are study-specific and not validated.

Willingness to Pay

A recent willingness to pay study has been published. The results of the meta-analysis of Davey et al and a contingent-valuation approach to determine willingness to pay were used. The authors found the average incremental benefit per patient for lispro over regular insulin was $39.31 Australian/month. Some significant demographic associations were found for willingness to pay including age, type of diabetes, education and income. However, the authors selected studies (six out of eight studies) from the meta-analysis rather than using the overall results. This resulted in a potential benefit of lispro (reduced hypoglycemia) not demonstrated in the original meta-analysis.
7. Other Issues

The cost associated with switching a patient from regular insulin to lispro has not been addressed by any study. There are a number of important issues associated with switching, including:

C Lispro’s short duration of activity may require increased doses of concomitant intermediate or long-acting insulin to prevent between meal hyperglycemia. The optimal basal dose of insulin to be used with lispro has yet to be determined.

C A change in meal plan may also be necessary when switching to lispro. Less snacking between meals may be needed, unless the next meal is delayed beyond the usual time, when an extra snack with or without an extra dose of lispro may be necessary. This regimen needs to be individualized.

C A patient’s daily routine, such as exercise schedules, may need to be adjusted when switching to lispro. Since the peak activity of lispro is reached more quickly, exercise within one hour of the meal may induce more hypoglycemia than with regular insulin. Exercise later after the meal (2 to 3 hours later) may result in less hypoglycemia.35

C No study has evaluated the costs associated with the treatment of hypoglycemia. There have been no evaluations of compliance and impact on subsequent glycemic control (and avoided morbidity), or of the impact on quality of life from averted hypoglycemic episodes.
8. Formulary Considerations

Does Lispro Have Any Unique Features?

C Due to the unique pharmacokinetic properties of lispro, it can be administered immediately before a meal. This may be useful for diabetic patients who cannot control or predict the timing of meals.

C In different clinical studies, lispro improved postprandial glucose profiles. However, its role in improving glycemic control based on HbA1c levels has not been fully established.

C There is no firm evidence to support a reduced frequency of symptomatic hypoglycemia by lispro treatment in patients with type I diabetes.

C The long-term safety profile of insulin lispro has not been established. In the United States it is not approved for use in children under 12 years of age, whereas in Canada there is no such limitation in the product monograph.

Does Lispro Show Incremental Benefit in Proportion to Incremental Cost?

Table 4. Comparative costs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Formulation</th>
<th>Cost*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin lispro</td>
<td>10 ml vial (100 U/ml)</td>
<td>$23.00/vial or 5 cartridges</td>
</tr>
<tr>
<td></td>
<td>1.5 ml cartridge (100 U/ml)</td>
<td>$46.00/5 cartridges</td>
</tr>
<tr>
<td></td>
<td>3 ml cartridge (100 U/ml)</td>
<td></td>
</tr>
<tr>
<td>Regular (Humulin-R)</td>
<td>10 ml vial (100 U/ml)</td>
<td>$15.51/vial</td>
</tr>
<tr>
<td></td>
<td>1.5 ml cartridge (100 U/ml)</td>
<td>$16.08/5 cartridges</td>
</tr>
<tr>
<td></td>
<td>3 ml cartridge (100 U/ml)</td>
<td></td>
</tr>
</tbody>
</table>

*Prices are based on The Ottawa Hospital price list.

Lispro costs one and a half times more than Humulin-R. Based on the available evidence, the only proven advantage lispro has over regular insulin is that it can be administered immediately before a meal. In an Australian pharmacoeconomic analysis using a willingness to pay approach, lispro was found to be the dominant strategy over regular insulin. The patient population included in the study was from a relatively higher social economic strata. These results may not apply to the patient population served by provincial drug plans in Canada, where there may be cultural and socioeconomic differences from the Australian population studied.
9. **Utilization**

A recent Patented Medicine Price Review Board (PMPRB) ruling has resulted in the reduction of the price of lispro (Humalog®) from $30.00 to $23.00 per vial.

The number of prescriptions for all forms of regular insulin has increased from 53,000 in 1993 to almost 68,000 in 1997 (Intercontinental Medical Statistics, IMS). This translates into $10.85 million and $17.97 million, respectively. Of the total prescriptions dispensed, approximately 50% are for the Lilly brand Humulin-R (IMS).

Lispro first appeared on the market in late 1996. In 1997 the drug had assumed 6.6% of the regular insulin market share, which translates into 12.9% of total dollars spent (based on the previous price of lispro). On a regional basis, it is now the third most common brand of regular insulin dispensed (exception: fourth in B.C.).

The table below represents the current formulary status of lispro (Humalog®). Four provinces provide the drug on their respective formularies, but under some restriction or altered status compared to regular insulin.

Table 5. Canadian Provincial Formulary Status of Lispro

<table>
<thead>
<tr>
<th>Province</th>
<th>Cover</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alberta</td>
<td>Yes</td>
<td>only pay up to the cost of Humulin-R; also cover seniors and members of the Provincial plan</td>
</tr>
<tr>
<td>British Columbia</td>
<td>Yes</td>
<td>only pay up to the cost of regular Humulin-R</td>
</tr>
<tr>
<td>Manitoba</td>
<td>Yes</td>
<td>only pay up to the cost of regular insulins</td>
</tr>
<tr>
<td>New Brunswick</td>
<td>No</td>
<td>formal criteria was not established by the Advisory Utilization Committee, requests have been considered on an exceptional basis under special authorization</td>
</tr>
<tr>
<td>Newfoundland</td>
<td>No</td>
<td>limited number of exceptions (approx. 6 to date) have been made under Special Authorization in very exceptional circumstances</td>
</tr>
<tr>
<td>Northwest Territories</td>
<td>Yes</td>
<td>only covered if an N.W.T. resident is registered under the Extended Health Benefits Program; residents can be provided with a maximum of a three month supply; anything over three months must be approved by the Department of Health and Social Services</td>
</tr>
<tr>
<td>Nova Scotia</td>
<td>No</td>
<td>only covered if ordered by an endocrinologist for non-senior patients that are undergoing intensive insulin therapy</td>
</tr>
<tr>
<td>Ontario</td>
<td>Yes</td>
<td>limited use benefit</td>
</tr>
<tr>
<td>Prince Edward Island</td>
<td>Yes</td>
<td>has been covered since March 1997; patients copay $10.00 per vial or box of cartridges of Humalog®, compared to $5.00 per vial or box of 1.5 ml cartridges of normal human insulins; implemented the double copay for Humalog® at the time Lispro was double the price of regular insulin</td>
</tr>
<tr>
<td>Quebec</td>
<td>Yes</td>
<td>restricted benefits</td>
</tr>
<tr>
<td>Saskatchewan</td>
<td>Yes</td>
<td>exception drug status for difficult to control diabetes</td>
</tr>
<tr>
<td>Yukon</td>
<td>Yes</td>
<td>covered under the Chronic Disease Program and the Pharmacare Program for Seniors</td>
</tr>
</tbody>
</table>
Current Provincial Formulary Status of Lispro

The table below is the updated formulary status of insulin Lispro (Humalog) based on information from the provincial drug plans as of July 27, 1999. This table is an update to table 5 of the CCOHTA report *Insulin Lispro: a critical evaluation*, 1999.

### Canadian Provincial Formulary Status of Insulin Lispro

| PROVINCE            | COVERAGE                  | DESCRIPTION                                                                 |
|---------------------|---------------------------|                                                                            |
| Alberta             | Yes                       | Open/general listing                                                      |
| British Columbia    | Exception Drug Status (EDS)| Maximum Allowable Cost (MAC) pricing up to the cost of Humulin R            |
| Manitoba            | Yes                       | Open/general listing                                                      |
| New Brunswick       | Special Authorization (SA)| SA based on a case by case basis                                           |
| Newfoundland        | Special Authorization (SA)| SA based on a case by case basis                                           |
| Northwest Territories| Exception Drug Status (EDS)| No criteria. Cover on a case by case basis for non-status individuals. Full coverage for status individuals. |
| Nova Scotia         | Exception Status (ES)     | Exception criteria for qualified clinical circumstances and at the written request of an endocrinologist |
| Ontario             | Limited Use (LU)          | Limited use benefit for qualified clinical circumstances                  |
| Prince Edward Island| Yes                       | Open/general benefit (same benefit as regular insulin)                     |
| Quebec              | Yes                       | Open/general listing                                                      |
| Saskatchewan        | Exception Drug Status (EDS)| For insulin pump users and for patients with difficult to control diabetes |
| Yukon               | Yes                       | Open/general benefit                                                      |
11. APPENDIX

Tables 2 and 3 summarize the published and unpublished studies available on lispro.

**Table 2. Studies Comparing Insulin Lispro (L) and Regular Insulin (R) among Patients with Diabetes Mellitus**

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of Patients, Type of Diabetes</th>
<th>Study Design</th>
<th>Duration of Treatment</th>
<th>Difference in 2-h Postprandial Increase in Glucose (mmol/l)</th>
<th>% Difference in HbA1c Level (mmol/l)</th>
<th>Difference in Frequency of Hypoglycemic Episodes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Garg et al³</td>
<td>39 IDDM</td>
<td>Parallel</td>
<td>1 year</td>
<td>-4.0 (p&lt;0.05)</td>
<td>+0.2 (NS)</td>
<td>-38/subject/year (p&lt;0.04)</td>
</tr>
<tr>
<td>Anderson et al⁴</td>
<td>1008 IDDM</td>
<td>Crossover</td>
<td>3 months</td>
<td>-2.0 (p&lt;0.001)</td>
<td>None</td>
<td>-0.8 /subject/30 days (p&lt;0.001)</td>
</tr>
<tr>
<td>Anderson et al⁵</td>
<td>722 NIDDM</td>
<td>Crossover</td>
<td>6 months</td>
<td>-1.6 (p&lt;0.001)</td>
<td>None</td>
<td>-0.26/subject/30 days (NS)</td>
</tr>
<tr>
<td>Anderson et al⁶</td>
<td>336 IDDM 295 NIDDM</td>
<td>Parallel</td>
<td>12 months</td>
<td>-0.8 (p=0.007) -1.0 (p=0.004)</td>
<td>-0.2 (p&lt;0.05) None</td>
<td>-0.1/subject/30 days,(NS) 0.1/subject/30 days,(NS)</td>
</tr>
<tr>
<td>Pfutzner et al⁷</td>
<td>107 IDDM</td>
<td>Crossover</td>
<td>3 months</td>
<td>-1.7 (p&lt;0.001)</td>
<td>None</td>
<td>-1.04/subject/month (p=0.008)</td>
</tr>
<tr>
<td>Vignati et al⁸</td>
<td>379 IDDM 328 NIDDM</td>
<td>Crossover</td>
<td>2 months</td>
<td>-2.5 (p&lt;0.001) -2.6 (p&lt;0.001)</td>
<td>None</td>
<td>0.1/subject/30 days, NS 0.0/subject/30 days, NS</td>
</tr>
<tr>
<td>Ronnenna and Viikari⁹</td>
<td>141 IDDM</td>
<td>Sequential</td>
<td>12 wk R then 12 wk L</td>
<td>NA -0.24 (N) -0.35 (L)</td>
<td>-0.76/subject/10 wk (p=0.005)</td>
<td></td>
</tr>
</tbody>
</table>

* All differences are the differences between treatment with insulin lispro and treatment with regular insulin.
Table 3. Unpublished Studies (Abstracts) Comparing Insulin Lispro and Regular Insulin among Patients with Diabetes Mellitus*+

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of Patients, Type of Diabetes</th>
<th>Study Design</th>
<th>Duration of Treatment</th>
<th>Difference in 2-h Postprandial Increase in Glucose (mmol/l)</th>
<th>% Difference in HbA1c Level (mmol/l)</th>
<th>Difference in Frequency of Hypoglycemic Episodes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crowley et al</td>
<td>86 IDDM 31 NIDDM</td>
<td>Crossover</td>
<td>6 months</td>
<td>-2.5 (p&lt;0.001)</td>
<td>None</td>
<td>-0.32/subject/30 days (NS)</td>
</tr>
<tr>
<td>Vignatil et al</td>
<td>167 IDDM</td>
<td>Parallel</td>
<td>1 year</td>
<td>-2.8 (p=0.001)</td>
<td>0.2 (p=0.031)</td>
<td>0.01/subject/30 days (NS)</td>
</tr>
<tr>
<td>Rowe et al</td>
<td>93 NA</td>
<td>Blinded, Crossover</td>
<td>3 months</td>
<td>-1.8 (NA)</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Schmitt et al</td>
<td>199 IDDM</td>
<td>Crossover</td>
<td>6 months</td>
<td>-1.1 (p&lt;0.001)</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Sindaco et al</td>
<td>12 IDDM</td>
<td>Parallel</td>
<td>3 months</td>
<td>-0.6 (p&lt;0.05)</td>
<td>-0.4 (p&lt;0.002)</td>
<td>-0.4/subject/month (NS)</td>
</tr>
<tr>
<td>Jansson et al</td>
<td>84 IDDM</td>
<td>Crossover</td>
<td>4 months</td>
<td>NS</td>
<td>-1.2</td>
<td>None</td>
</tr>
</tbody>
</table>

*All differences are the differences between treatment with insulin lispro and treatment with regular insulin.

+ Regimens involved multiple daily doses
IDDM= Insulin dependent diabetes mellitus   NIDDM= Non-insulin dependent diabetes mellitus   NS= not significant   NA= Not available
12. References


